Thomas Tarenzi – ESR14

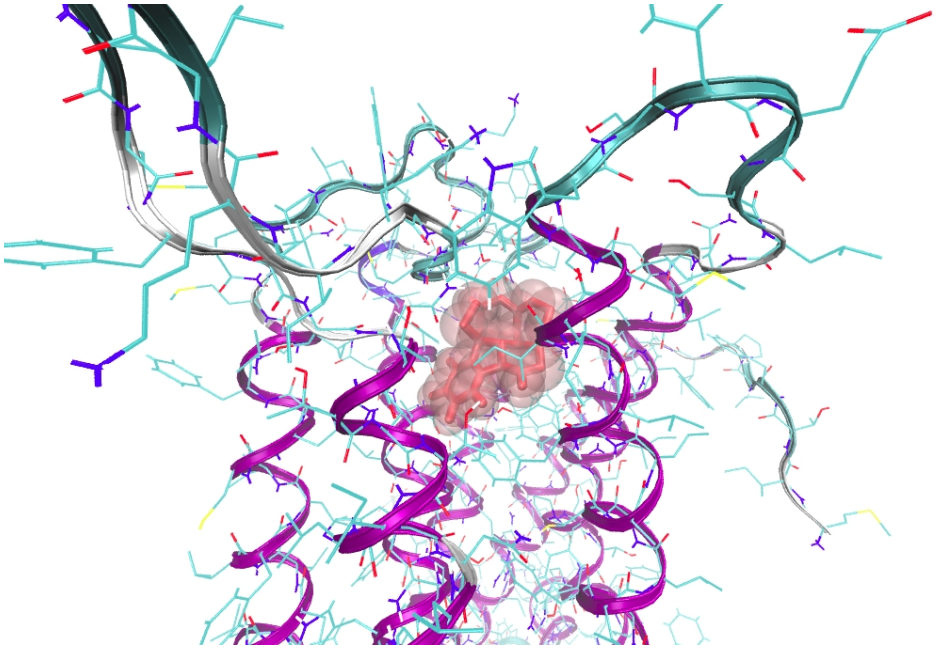
"Targeting G-protein-coupled receptors (GPCRs) for pharmaceutical intervention"

Awarding Institutions : **CyI** and **RWTH**

Supervisors : Prof. G. Christophides,

Prof. P. Carloni

Co-supervisor : Dr. V. Calandrini



HPC-LEAP EUROPEAN JOINT DOCTORATES

THE CYPRUS INSTITUTE

RWTH AACHEN UNIVERSITY

Educational background

- **University of Parma**

  Bachelor degree in Chemistry.

  "*Synthesis of PNA monomers doubly functionalized*". Supervisor: Prof. R. Corradini

- **University of Florence**

  Master degree in Chemistry of biomolecules.

  "*Just flexible linkers or important functional modules?*

  The high-resolution NMR investigation of a disordered domain of CBP".

  (Piai A., Calcada E., Tarenzi T. et al., *Biophys. J.*, 2016)

  Supervisors: Prof. I. C. Felli, Prof. R. Pierattelli

Broad interest in the fields at the interface between **bio-organic chemistry**, **biophysics** and **computer science**.

Training, outreach and dissemination

Training:

- 4 HPC-LEAP workshops.
- Thematic HPC-LEAP workshop in Computational Biology and applications in human health.

Conferences:

- NIC Symposium, Forschungszentrum Jülich, Germany.
- CECAM workshop "Structural and Functional Annotations of Bioinorganic Systems", Pisa, Italy.
- INM Retreat, Forschungszentrum Jülich, Germany.
- IAS Symposium, Forschungszentrum Jülich, Germany.
- Workshop "Hybrid Methods in Molecular Simulations", Cagliari, Italy.

Proposals:

- JARA-HPC, RWTH Compute Cluster (Aachen, Germany) - **349 992 core-h** awarded.
- OcuLUS Cluster (Paderborn, Germany) – **864 000 core-h** awarded.

Publications:

- Tarenzi Thomas, Calandrini Vania, Potestio Raffaello, Giorgetti Alejandro, Carloni Paolo, "Multiscale simulation approach for accurate drug affinity predictions using low-resolution protein models", *Current Pharmaceutical Design* (***submitted***)

Goal of the project

Development of a **computational method** to accurately predict **binding poses** and **ligand affinities** of ligands binding to membrane proteins for which experimental information is not available.

Focus on GPCRs

- Largest membrane-bound receptor family in mammals.
- Widespread biological functions.
- Target for ca. 40% of FDA-approved drugs.

Crucial role in controlling infection responses in **malaria vector mosquitoes**.

Structural information is laking for about 95% GPCRs

+

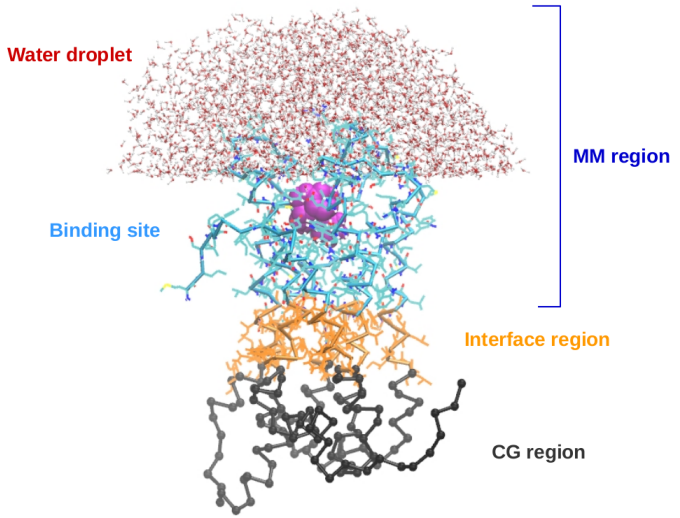
Low sequence identity

Limitation of traditional bioinformatic approaches

Need to develop specific GPCRs-targeting *in silico* tools.

Multiscale approach for drug-affinity predictions

Molecular Mechanics/Coarse-grained approach

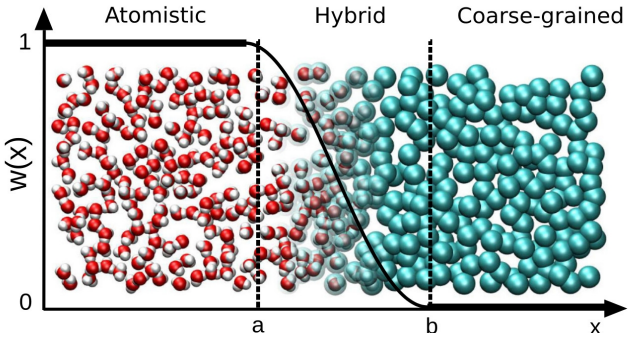


Leguebe M. et al., *PLOS ONE* (2012)

Hamiltonian-Adaptive resolution scheme

$$H = K + V^{p/p-w} + \sum_{\alpha}^{N}\left\{\lambda_\alpha V_\alpha^{MM} + (1-\lambda_\alpha)V_\alpha^{CG}\right\} - \sum_{\alpha}^{N}\Delta H(\lambda_\alpha).$$

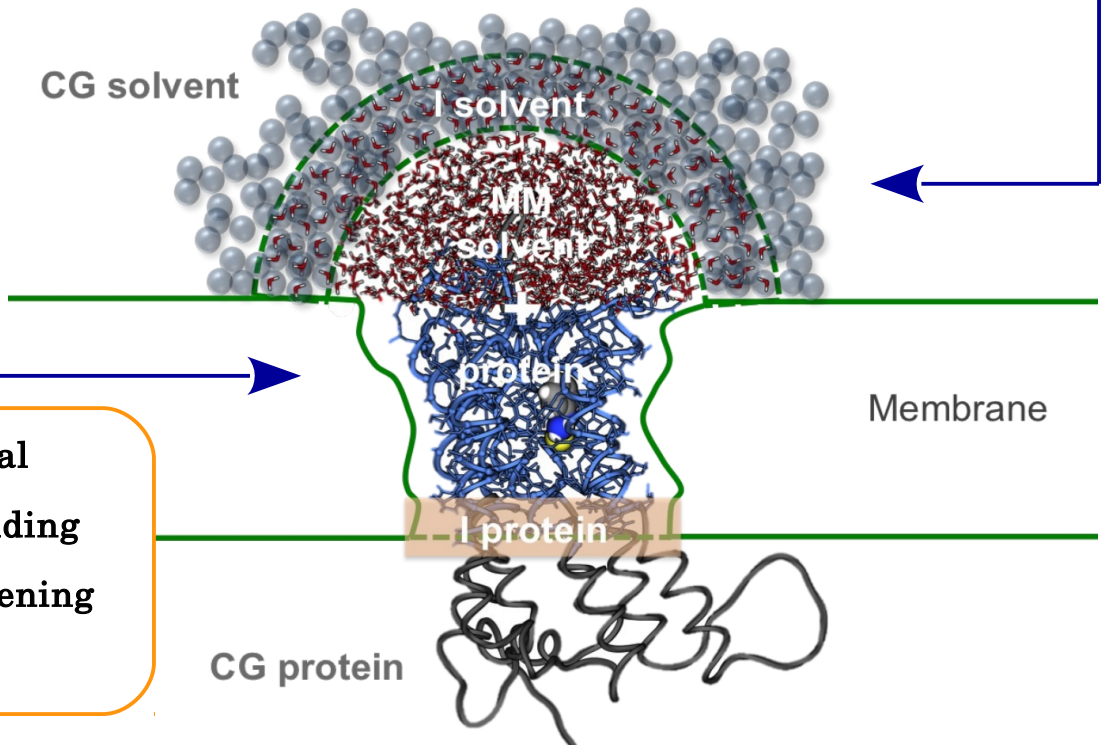
$$\Delta H(\lambda_\alpha) = \frac{\Delta F(\lambda_\alpha)}{N} + \frac{\Delta p(\lambda_\alpha)}{\rho_0} \equiv \Delta\mu(\lambda_\alpha) = \frac{\Delta G(\lambda_\alpha)}{N}.$$



Potestio R. et al., *Phys. Rev. Lett.* (2013)

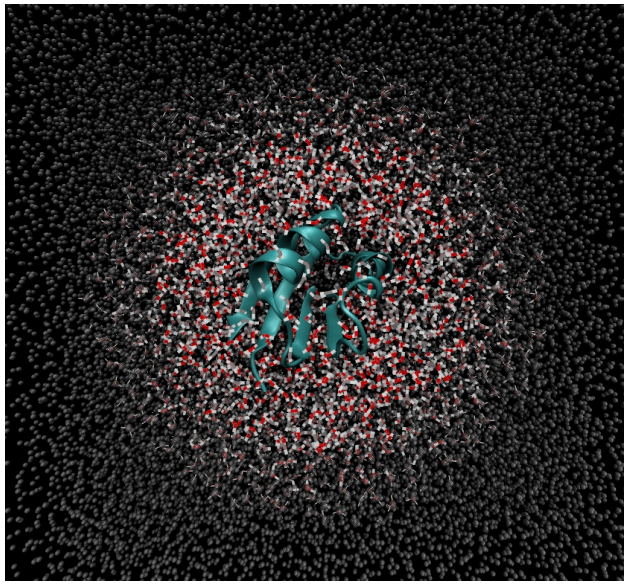
Dual-resolution ***protein***

Dual-resolution ***solvent***

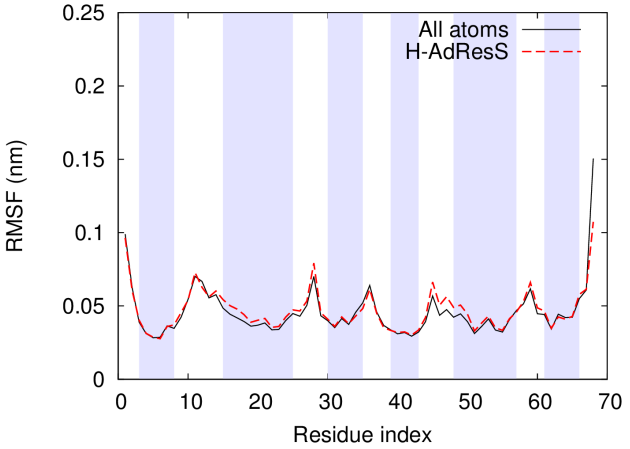


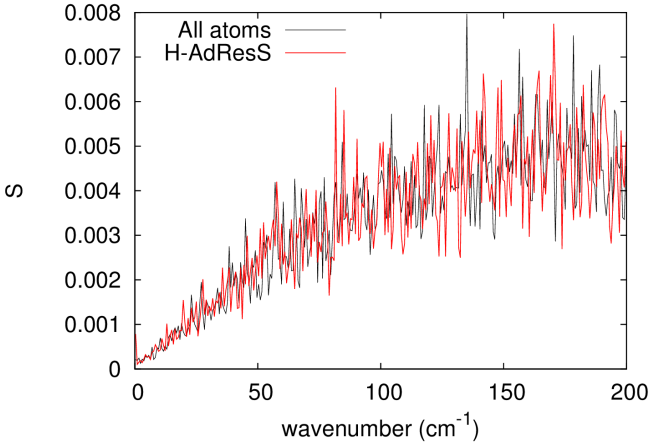
Simulation of a **grand canonical ensemble** for calculation of **binding free energies** and **ligand screening** (need for **HPC resources**).

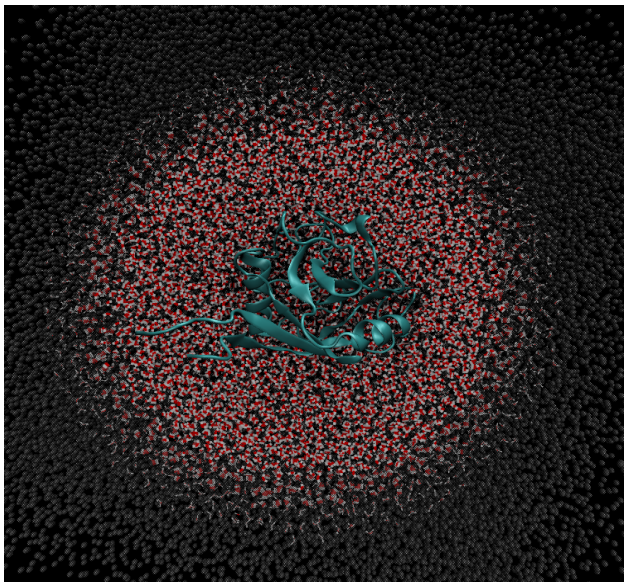
Step n° 1: application to cytoplasmic proteins



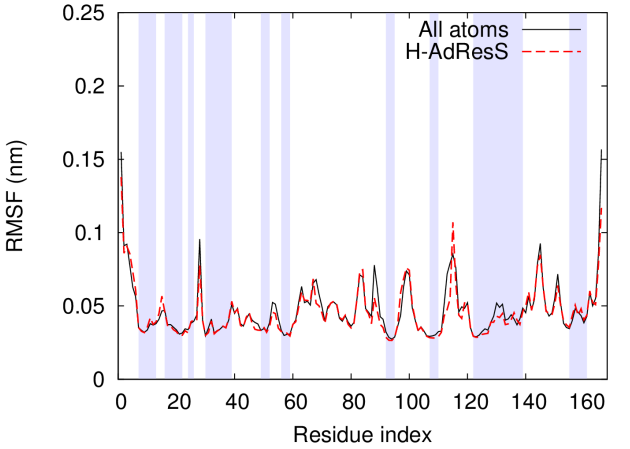
Human **apo-Atox1** - Protein properties (structure/dynamics)

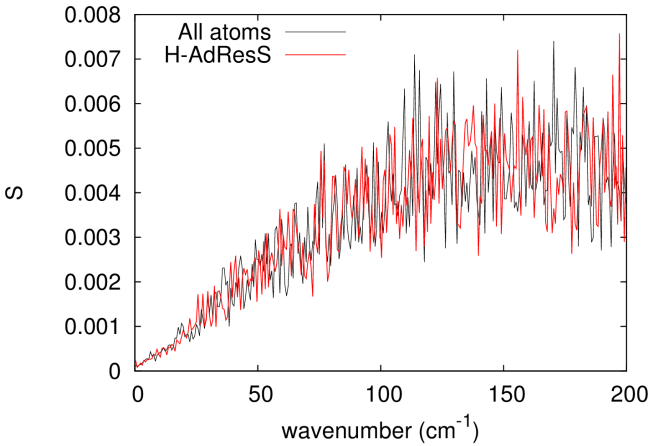






Human **Cyclophilin J** – Protein properties (structure/dynamics)

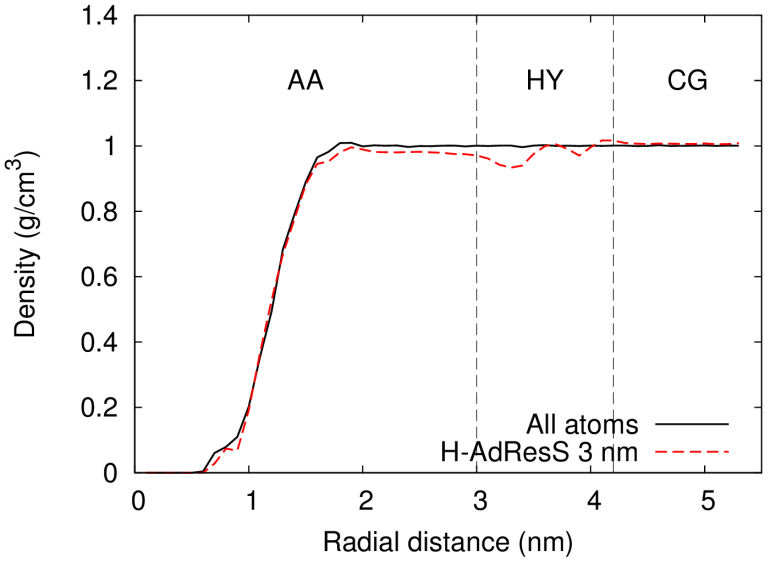




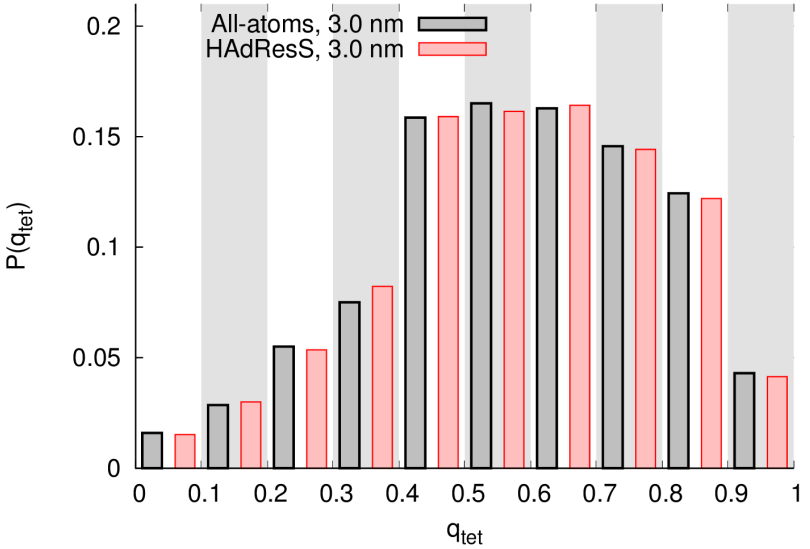
Application to cytoplasmic proteins

Water properties (results are reported for the atox1 system):

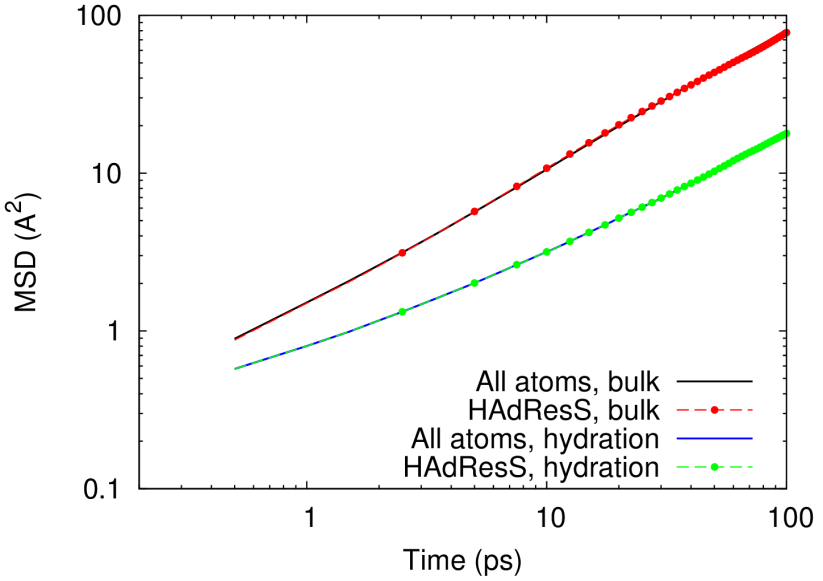
a. *Density*



b. *Local angular order*



c. *Dynamics*

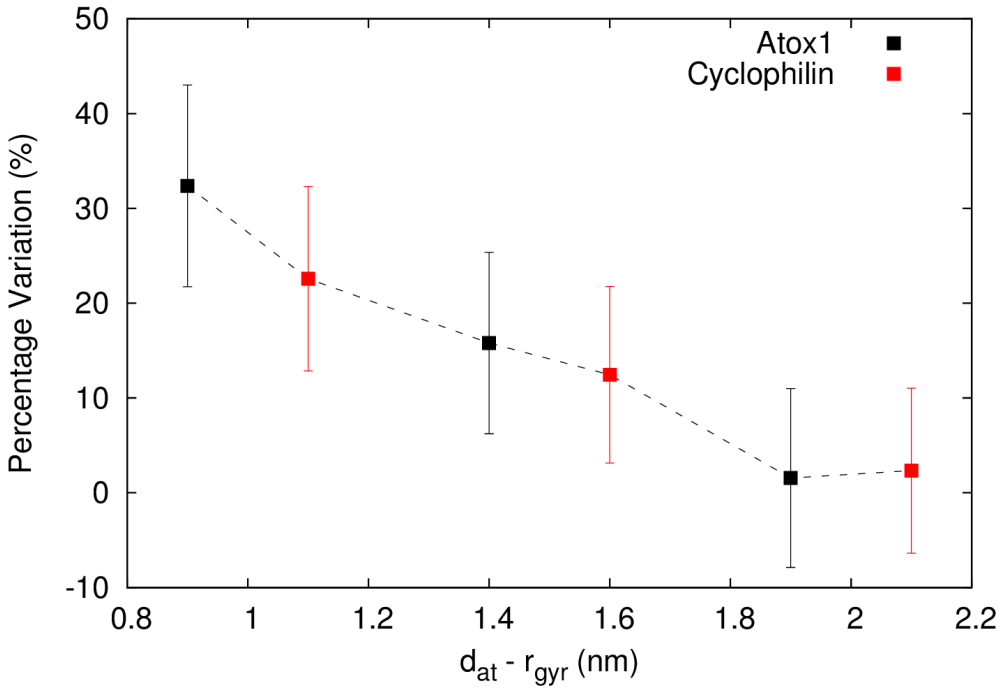


Structural and dynamical properties of atomistic water are preserved on passing from all-atom MD to H-AdResS MD.

However, we must be careful about the size of the atomistic region.

Application to cytoplasmic proteins

Decreasing the atomistic region size:



Percentage variation of the **reorientational times** of hydration water in H-AdResS simulation relative to the all-atom ones, as a function of the distance between the radius of gyration of the protein and the border of the atomistic region d_{at}.

$$d_{at} - r_{gyr} > 1.6 \text{ nm}$$

Future work

- The new approach will be fully tested on GPCR/ligand complexes for which atomistic structures are available, using atomistic simulations as a reference.

- Application of the tested code on GPCR/ligand complexes relevant for ***malaria transmission***, in order to predict binding poses and ligand affinities.

This will lead to interactions with the group of Prof. G. Christophides.

Acknowledgement

Prof. Dr. Paolo Carloni

Prof. Dr. George Christophides

Dr. Vania Calandrini

- Thanks to all the staff at the IAS-5/INM-9 in Forschungszentrum Jülich.

Thank you for your attention.

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